ORIGINAL ARTICLES

PROBLEMS OF ADRENAL INSUFFICIENCY*

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DISTURBANCES IN PHYSIOLOGY

THOMAS ADDISON, in 1855, pointed out for the first time that "universal disease of the capsules" is incompatible with life and stated that aside from this observation the function of these structures "is almost, or altogether, unknown." At the same time, Addison predicted that the further study of disease of the adrenal glands might lead to some understanding of their physiological activity. This prophecy has in recent years been amply fulfilled and it is to a consideration of problems of the functions of the cortex of the adrenal glands and the treatment of adrenal insufficiency that I should like to call your attention.

The physiological disturbances known to be present in adrenal insufficiency may be divided into two general categories. The first of these groups of disturbances is associated with abnormalities in behavior of certain of the electrolytes and water. The disturbances are, in part, reflected by the changes in concentration of certain substances in the blood serum in patients suffering from "decompensated" Addison's disease as shown in the slide. Among the abnormalities to be observed are a decrease in the sodium concentration, an increase in potassium, retention of nonprotein nitrogen, and an increase in serum protein concentration associated with loss of water from the blood. These changes which appear to have as their point of departure an abnormally great loss of sodium salts and water through the kidneys give rise to a decrease in renal function as characterized by diminution in creatinin and urea clearances as well as a decrease in ammonia excretion by the kidney. It seems highly probable that these changes in renal function can be attributed to a decrease in plasma volume and a consequent decrease in renal blood flow. Whether or not specific changes in the cells of the renal tubules also contribute to these changes in renal function as they probably do in relation to the disturbances in sodium, potassium and water, we do not know. The development of hypotension which may reach extraordinarily low levels in the crises is also in part to be attributed to the disturbances of salt and water metabolism. The clinical significance of the sodium ion and water in relation to this category of disturbances in adrenal insufficiency was first demonstrated by the group working at the Presbyterian Hospital in New York nine years ago at which time we found that the simple procedure of the restriction of the amount of sodium chlorid in the diet would induce an alarming adrenal crisis in a well-compensated Addisonian patient and that the administration of salt without the aid of other procedures would frequently alleviate this condition.

The second category of physiological disorders demonstrable in adrenal insufficiency is that dependent upon abnormalities of carbohydrate metabolism. In 1909 Porges first demonstrated the presence of hypoglycemia both in patients with Addison's disease and in adrenalectomized animals. At that time this disturbance was thought to be due to destruction of the adrenal medulla. Later Britton and Silvette, on the basis of extensive experiments, maintained that the disturbances present in carbohydrate metabolism resulted from cortical rather than medullary adrenal insufficiency. This point of view was not accepted by most workers in the field but in recent years it has received ample confirmation on the basis of the studies of C. N. H. Long and his coworkers, by the studies of Kendall and others at the Mayo Clinic, and by Thorn and his associates in Baltimore. In patients with Addison's disease, disturbances of carbohydrate metabolism are manifested by mild spontaneous hypoglycemia which is demonstrable in most patients at some time and which is severe in about 25 per cent of the cases. Striking sensitivity of Addisonian patients to small doses of insulin offers further evidence of disturbed carbohydrate metabolism. It is possible that some of the feeling of muscular weakness exhibited by Addisonian patients as well as some of the diffuse and focal neurological disturbances occasionally encountered result, at least in part, from disturbances in carbohydrate metabolism. In animals, particularly in the cat and rat, the tendency to hypoglycemia and insulin sensitivity following adrenal ablation occurs with greater regularity than it appears to do in man and in the operated dog.

The influences of the adrenal cortex upon carbohydrate metabolism are readily demonstrable in the rat. Thus Long and also Kendall and his coworkers find that the administration of adrenal cortical extract to normal mice and rats increases glycogen storage in the liver. They have also shown in partially pancreatectomized animals that the administration of cortical extract increases glycosuria and nitrogen excretion and they have also demonstrated in phlorizinized animals that the excretion of glucose and nitrogen increases in such a way that the complete D/N ratio of about 3.4 is developed. In other words it appears as though adrenal cortical extract in these animals acted as "anti-insulin." It remains for the future to determine whether or not these changes in carbohydrate metabolism initiated by adrenal cortical hormones are due to a direct effect on carbohydrate metabolism resulting from a decrease in its utilization or whether these hormones influence carbohydrate metabolism indirectly by increasing protein breakdown and glucose formation, i. e., gluconeogenesis, as suggested by Long.

Intimately related to the disturbances in carbohydrate metabolism observed in adrenalectomized animals is the capacity for physical work. Ingle has shown repeatedly that the steroids of the adrenal

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cortex which have the greatest effects upon carbohydrate metabolism are the same as those which have the greatest effect in restoring the "work capacity" of the adrenalectomized rat. Ingle has also shown that this "work capacity" of the adrenalectomized rat is only slightly increased by the life-maintaining hormone which has its effects only on electrolyte and water metabolism.

In the foregoing discussion I have dealt with the two categories of disturbances known to be present in adrenal insufficiency. I should like now to speculate briefly concerning the possibility of a third category. A certain number of patients with Addison's disease die with what appears to be typical Addisonian death characterized by profound asthenia, falling blood pressure and a small or soft pulse. These changes may develop without apparent relation to the state of the electrolyte and water metabolism and are apparently unrelated to the level of the blood sugar. Furthermore, these patients, at times, fail to respond to what may be considered adequate therapy with active hormonal substances as judged by their effects on the water content of the blood, concentration of electrolytes in the blood and the maintenance of blood sugar. In other words a number of patients die Addisonian deaths usually associated with a terminal rise in temperature and a sharp decrease in blood pressure but without the expected chemical changes. Whether these patients suffer from a central disturbance of the vasomotor apparatus or from purely peripheral vasomotor changes is not apparent, but it seems fairly certain that a disturbance of the vasomotor system is present. Whereas this possibility is speculative, it seems important that it be borne in mind, and that we recognize that disturbances apart from the two categories described may exist.

Before proceeding to a discussion of therapy I should like to consider briefly the present state of our knowledge concerning the steroids of the adrenal cortex and their physiological effects. At the present time, more than twenty of these substances have been isolated from adrenal glands in crystalline form. Of these, there are four with demonstrable physiological activity. It is of great interest that the nature of the physiological activity is dependent upon the chemical structure in general and upon the number and location of oxygen atoms in particular. Thus, desoxycorticosterone, the only steroid thus far synthesized and the only one available commercially, has striking effects upon electrolyte and water metabolism and it has no significant effect upon carbohydrate metabolism. On the other hand corticosterone, dehydrocorticosterone and "compound E" of Kendall, which is 11-dehydro-17-hydroxycorticosterone, contain four or five oxygen atoms and have striking effects upon carbohydrate metabolism in rats and only slight effects upon salt and water metabolism. Of the carbohydrate-active steroids "compound E" of Kendall has the greatest potency. The steroid residue which remains after the extraction of the crystallizable compounds from adrenal glands has, curiously enough, a life-maintaining activity greatly in excess of that of desoxycorticosterone. Whether or not the various steroids isolated represent degradation products of one "mother compound" is not known at the present time. In other words, there remain tasks for the chemists in the isolation of other active compounds and in the synthesis of any with an effect on carbohydrate metabolism.

TREATMENT

I should like now to consider the problem of the treatment of Addison's disease. The treatment of Addison's disease, like that of diabetes mellitus, should be directed primarily toward (1) the specific replacement of the hormone or hormones lacking, (2) the correction of the physiological disturbances which ensue as a consequence of this endocrine deficiency, and (3) the avoidance of factors known to intensify manifestations of the disease. The nature of the therapy and the vigor with which it must be applied vary tremendously with the phase of the disease present. In the patient whose disease is well compensated, a few general measures such as the avoidance of physical and mental fatigue, the immediate care of even mild acute infections, and the ingestion of a liberal amount of sodium chlorid will suffice to maintain moderately good health for periods of months or even years. On the other hand, with the appearance of a crisis, whether it occurs in the natural progression of the disease or whether it results from known causes, a number of active therapeutic measures may have to be applied promptly and intensively in order to combat successfully the grave and often fatal loss of inorganic base with its attendant dehydration and peripheral circulatory collapse. Procrastination and inadequate treatment of the crisis sacrifices patients who might otherwise be restored to a useful existence.

At the present time three therapeutic agents are at our disposal in the treatment of established adrenal insufficiency, i. e., Addison's disease. These include (1) sodium salts, (2) desoxycorticosterone esters, and (3) adrenal cortical extracts. The results which may be anticipated with these various therapeutic agents are naturally dependent upon their effectiveness in correcting the physiological disturbances known to be present. Thus it might be expected that salt and desoxycorticosterone would tend to rectify the disorders of electrolyte and water metabolism. It might be expected also that cortical extract which contains a mixture of steroids, would correct disturbances in carbohydrate metabolism as well as those of salt and water and in addition increase muscular strength.

The results of treatment of one patient, I might add the first in whom salt treatment was tried, are shown on the slide. These results have been duplicated on many occasions in many patients and are probably familiar on the basis of your own experiences. Patients receiving salt for the purpose of maintenance usually require 10 to 18 grams a day in enteric-coated tablets or in 1 per cent solution. Only a few are able to tolerate large amounts of salt in capsule form. In a crisis, infusions of 3 to 4 liters of normal salt solution a day are usually necessary to relieve extreme weakness, marked

hypotension and gastric intolerance. It is rather surprising how frequently this simple form of therapy meets with success in restoring a critically ill Addisonian patient to relatively good health and how effective it proves in maintaining a normal electrolyte pattern in the blood in the majority of patients with disease of the adrenal cortex. On the other hand the limitations of salt therapy are made apparent by the fact that only three of a group of approximately 30 patients in our clinic are now being continued on this regime. These three patients have had the diagnosis established either by having a crisis induced through salt withdrawal or by admission to the hospital with spontaneous adrenal cortical decompensation. These patients who have been on salt for 7½, 6 and 1½ years respectively are able to work and cannot be persuaded to use synthetic hormones. Many patients who were formerly maintained on salt alone are now receiving synthetic hormone and have shown further improvement.

This brings us to a consideration of the effects and limitations of treatment with desoxycorticosterone. This steroid was both isolated and synthesized by Reichstein in Zurich in 1937. Desoxycorticosterone acetate is, as you know, administered subcutaneously or intramuscularly in an oil medium, or by pellet implantation as first practiced by Levy-Simpson in England and by Thorn in this country or by sublingual instillation in a solution of propylene glycol as recently recommended by Doctor Anderson in San Francisco. The striking physiological activity of desoxycorticosterone in patients with Addison's disease is summarized in the slide. In addition to the changes shown there are obvious changes in electrolyte excretion, i. e., sodium chlorid retention and augmentation of potassium excretion. It should be pointed out that there is a wide difference in the response of patients to desoxycorticosterone and that the reasons for these differences are not apparent. For example, one of our patients gained 11 kilos in ten days. Another patient on the identical regime gained only 2 kilos in thirty days even though his dosage of hormone was greater. In connection with the effect of this hormone on salt and water retention, it is of interest that we have encountered patients in whom it has been impossible to raise the blood sodium level to normal although the capacity for salt and water retention and edema formation appeared unlimited.

Desoxycorticosterone, as has been stated, has no demonstrable effects on carbohydrate metabolism and its effect on pigmentation is doubtful.

It is beyond the scope of this paper to discuss details of therapy but it may be stated that most Addisonian patients require a maintenance dose of desoxycorticosterone varying between 1 and 7 milligrams daily given subcutaneously and without the addition of salt beyond that present in the usual diet. On this regime most patients have made extraordinary gains as far as their sense of well-being, their strength, their appetite, their weight, and their outlook on life are concerned. Some are at work and others are, from the point of view of strength, capable of undertaking their normal activities.

It is virtually impossible to lay down general rules for treatment in a situation in which the responses of patients vary as widely as they do in acute adrenal insufficiency, i. e., in severe crises. With this viewpoint in mind, I cannot be more specific than to say that 10 milligrams of desoxycorticosterone in oil given twice a day and repeated infusion of glucose in normal saline often constitute the treatment needed to restore the patient. In any event constant vigilance is required to steer a course midway between undertreatment and overdosage with the hormone.

Two years ago we reported the clinical and physiological evidences of overdosage with desoxycorticosterone therapy. The subjective evidence consists of increasing puffiness of the face, swelling of legs or even anasarca, tightness in the chest, palpitation, dyspnea and orthopnea, weakness and sometimes headache. Objectively the signs are those of congestive heart failure with fluid accumulation, enlargement of the heart, congestion of the lungs, increase in venous blood pressure, decrease in vital capacity, and increase in the cardiac silhouette as revealed by x-ray. The blood may show strikingly hypoproteinemia and the potassium content of the serum may be sharply reduced. In the control of therapy, the rapid gain in weight, the development of edema, pulmonary râles, decrease in vital capacity and decrease in serum protein below about 5.5 per cent constitute the most practical signs of overdosage. Recently, we have attempted without success to reproduce this syndrome of fluid retention and cardiac failure in dogs. Instead, normal dogs receiving large doses of desoxycorticosterone in the course of two weeks develop two different but equally dramatic syndromes. One of these bears resemblance to diabetes insipidus. The other syndrome is that of intermittent periodic paralysis characterized by marked weakness of the neck and leg muscles associated with a sharp decrease in serum potassium concentration. This syndrome can be prevented or relieved by the administration of potassium salts. The muscles in the paralytic dogs who ultimately die of this disorder show a curious fragmentation of muscle fibers, and on chemical analysis the muscles are found to have as much as 30 per cent of the intracellular potassium replaced by the sodium ion.

Having discussed the rôle of salt and desoxycorticosterone in the treatment of adrenal insufficiency, I should like to mention the action of cortical extract and one of the crystalline steroids, i. e., corticosterone, which is isolated from the adrenal glands, and which in animals affects carbohydrate metabolism and "work capacity."

Through the courtesy of the Roche-Organon Laboratories, which have provided us with all of our adrenal preparations, we were able last year to compare the effect of desoxycorticosterone, corticosterone and cortical extract upon electrolyte and carbohydrate metabolism. For this purpose one of our Addisonian patients was maintained on a constant metabolic regime and was given 6 milligrams

of desoxycorticosterone daily, i. e., enough to prevent the development of acute cortical insufficiency. After adequate control observation he was given an additional dose of 20 milligrams of desoxycorticosterone daily for a period of 5 days and after two more 5-day periods on the standard régime he received 18.2 milligrams of corticosterone daily for 5 days. After further control periods he was given 21 cubic centimeters of cortical extract daily. From the slide it will be seen that desoxycorticosterone had a striking effect upon sodium excretion and less upon potassium excretion. Whereas corticosterone and cortical extract had demonstrable effect in the same direction, they were insignificant in comparison with desoxycorticosterone. Thorn had shown earlier that cortical extract influenced electrolyte excretion in patients with Addison's disease, but he too showed that enormous amounts are necessary to produce a very small effect. Thus it is apparent that cortical extract has little to recommend it for the correction of salt and water disturbances in comparison with desoxycorticosterone.

As has been stated, it might be anticipated that cortical extract and corticosterone would have a greater effect upon carbohydrate metabolism than would desoxycorticosterone. In our studies, no difference was observed in their influence upon the fasting respiratory quotient. The effects on glucose tolerance curves are shown in the slide. In the light of our knowledge of the effects of corticosterone and cortical extract upon carbohydrate metabolism in rats, it seems possible that the difference in sugar curves obtained by us with the patient on a constant régime may have some significance, but it certainly is not enough to be of clinical value since, at the end of three hours, the blood sugar level fell to about 50 milligrams per cent with all preparations.

On the basis of these studies we are forced to the conclusion that the virtues of cortical extract over those of desoxycorticosterone are essentially theoretical and that small doses of extract, i. e., less than 5 cubic centimeters, have probably little effect unless it be psychological. It is possible that cortical extract may contain some substance, the physiological activity of which we cannot yet measure. I say this because of the fact that some patients receiving this preparation maintain that they "feel better" even though no demonstrable chemical or physiological change can be observed. The unsatisfactory nature of this type of evidence is obvious, but perhaps is deserving of some consideration.

This brings me to one point of general interest which I should like to discuss before closing. We all encounter a large number of patients who complain of the syndrome characterized by exhaustion, fatiguability and anorexia associated with varying degrees of hypotension. This exhaustion state appears in the course of malignant disease, it is often encountered during and after acute or protracted infectious diseases, it follows serious surgical procedures with considerable regularity, it frequently follows severe emotional strain and is occasionally encountered without any known association. Whether or not this exhaustion syndrome has a single underlying physiological basis, I do not know. The question which concerns us is whether it may be ascribed to "functional adrenal insufficiency." This I also do not know. In contrast to patients with unequivocal adrenal insufficiency these patients show no evidence of disturbances of electrolyte and water metabolism either spontaneously or as a result of salt withdrawal. Nor is there any apparent disorder of carbohydrate metabolism, and yet their symptoms are often more intense than are those of patients with only partially controlled Addison's disease. On the other hand, Weil and Browne have shown that the urine obtained from patients who have undergone operation or who have acute infections contains substances which protect young adrenalectomized rats from the fatal effects of chilling as does adrenal cortical extract, whereas the extract of normal urine possesses no such properties. These studies do not establish the fact, however, that the substances recovered from the urine of patients under various types of stress are adrenal in origin.

I fear that the ultimate solution of the problem of exhaustion states as well as many other problems mentioned this morning must be left to the future.

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SURGICAL LESIONS OF THE ADRENAL GLANDS*

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THE development which has occurred in the recognition of certain surgical lesions of the ductless glands has resulted from a combination of studies by clinician, internist and experimenter. The enthusiasm of each in turn aroused the others, with the result that all have become endocrine conscious. In spite of the tendency to overestimate the value of certain of the hormones and glandular preparations, endocrinologic studies have resulted in brilliant achievements in diagnosis, therapy and pure science.

Diseases of the ductless glands usually are accompanied by quantitative and, possibly, by qualitative alterations in secretory activity. In the adrenal glands or in the pituitary body, in each of which the gland is composed of two or more separate functional units, the disease may be manifested by clinical pictures which suggest hyperfunction of one unit and hypofunction of the other. These mixed types of conditions may be exceedingly difficult to interpret on a physiologic basis. Further adding to the complexities of the problem is the fact that patients who present endocrine disturbances may be suffering from associated abnormalities of one or more of the ductless glands as well.

Clinically and experimentally, Marine and Jaffe have shown that an intimate relationship exists

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